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(54) **Topical antimicrobial pharmaceutical compositions.**

- (57) A topical antimicrobial pharmaceutical composition comprising a tertiary mixture comprising:
- (a) a glyceryl fatty acid ester;
  - (b) a mixture of fatty acids comprising:
    - (i) a first fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
    - (ii) a second fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
  - (c) a pharmaceutically acceptable carrier.

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The present invention relates generally to topical pharmaceutical compositions and, more particularly, to primarily aqueous solutions exhibiting unique antimicrobial properties.

The use of antimicrobial agents plays an important part in current medical therapy. This is particularly true in dermatology, where the most effective course of treatment for skin, mucous membranes, hair lesions, or infections frequently includes the use of a topical antimicrobial agent. The present invention includes topical compositions and methods which provide unique performance against a broad spectrum of microbes with excellent speed.

Various carboxylic acids are known to be good antimicrobial agents. However, when these acidic solutions are directly applied to an animal's skin, they may interfere with wound healing, cause irritation, inflammation or the like. Also, these solutions have poor solubility properties in water which, in turn, limits the efficacy of aqueous solutions employing these materials.

It is also well recognized that there is presently a need for a mild antimicrobial which can be safely applied to skin and mucous membranes, such as an animal's teats, ears and eyes, that will be substantially harmless to the applied area but which will eliminate, arrest, or substantially reduce the growth of bacteria, fungi, mold and the like. The instant invention meets this need.

The art discloses that several different carboxylic acid are generally useful in the suppression of fungi, bacteria, molds and the like growth. United States Patent No. 4,406,884 issued to Fawzi discloses a topical antimicrobial composition in the form of an aqueous gel or lotion. This composition contains C<sub>5</sub>-C<sub>12</sub> fatty acids and has a pH no greater than about 5. United States Patent No. 4,343,798 issued to Fawzi, teaches a topical antimicrobial anti-inflammatory composition having a pH less than about 5 and containing C<sub>5</sub>-C<sub>12</sub> fatty acids together with a corticosteroid component. United States Patent No. 4,489,097 issued to Stone, teaches the addition of anti-fungal/antibacterial materials to sterile compositions. The antifungal/antibacterial material disclosed is a C<sub>4</sub>-C<sub>9</sub> carboxylate antimicrobial agent having a pH of about 6.0 or below. United States Patent No. 4,410,442 issued to Lucas, et al. teaches solutions for use with hydrophilic soft contact lenses containing C<sub>5</sub>-C<sub>12</sub> fatty acids, especially octanoic acid. United States Patent No. 4,392,848 issued to Lucas, et al. teaches a catheter having a liquid reservoir of an antimicrobial agent flowing through the lumen of the catheter. The antimicrobial agent disclosed is a straight-chain carboxylic acid or carboxylic acid salt having a C<sub>4</sub>-C<sub>9</sub> chain. United States Patent No. 4,430,381 issued to Harvey, et al. teaches a process for imparting antimicrobial properties to a material. The antimicrobial being a C<sub>3</sub>-C<sub>12</sub> alkane, alkene or alkyne monocarboxylate. United States Patent Nos. 4,343,788 and 4,479,795, both issued to Mustacich, et al. teach medical polymers that provide diffusion for certain carboxylate antimicrobial agents. United States Patent No. 4,002,775 issued to Kabara teaches a food grade microbicidal composition having a monoester with a C<sub>12</sub> aliphatic fatty acid as its primary microbicide. United States Patent No. 1,772,975 issued to Weiland teaches the use of lactic acid, acetic acid, or combinations thereof, as antiseptics at properly adjusted pH levels. United States Patent No. 2,154,449 issued to Hoffman et al. teaches the use of aliphatic C<sub>3</sub>-C<sub>12</sub> carboxylic acids and their salts as mold inhibitors in food compositions. United States Patent No. 2,190,714 issued to Hoffman, et al. teaches the addition of a C<sub>3</sub>-C<sub>12</sub> carboxylic acid to inhibit growth food products other than margarine and sourdough bread. United States Patent No. 3,404,987 to Kooistra, et al. teaches an antimicrobial containing edible mineral salt and edible acid preservative substances, particularly propionic acid. United States Patent No. 2,466,663 issued to Russ, et al. teaches the use of a topical or intravenous caprylic acid solution to combat mycotic infections or growths. United States Patent No. 2,729,586 issued to Peck teaches a therapeutic compositions having at least one salt of a C<sub>3</sub>-C<sub>11</sub> monocarboxylic acid and water soluble chlorophyll.

Other materials also disclose the use of fatty acids for the suppression of fungi, bacteria, mold and the like. Kabara, J., Medium-chain Fatty Acids and Esters as Antimicrobial Agents, Cosmetic and Drug Preservation, Pgs. 275-304, 1984, teaches the use of C<sub>6</sub>-C<sub>22</sub> saturated and unsaturated fatty acids as antimicrobials. Kabara, J., Toxicological, Bactericidal and Fungicidal Properties of Fatty Acids and Some Derivatives, The Journal of the American Oil Chemists' Society, Vol. 56, No. 11, Pages 760A-767A (1979) teaches the applying of fatty acids to animal skin and eyes. Some fatty acids were found to be skin and eye irritants. Kabara, J., Inhibition of Staphylococcus Aureus In a Model Agar-Meat System By Monolaurin: A Research Note, Journal of Food Safety, Vol. 6, Pgs. 197-201 (1984), teaches the use of monolaurin as a food preservative to combat microorganisms. Kabara, J., Antimicrobial Agents Derives from Fatty Acids, JAOCS, Vol. 61, No. 2, Pgs. 397-403 (1984) teaches the use of saturated and unsaturated fatty acids as antimicrobial agents. Kabara, J., GRAS Antimicrobia Agents for Cosmetic Products, Journal of the Society of Cosmetic Chemists, Vol. 31, Pgs. 1-10 (1980), teaches the composition of monolaurin, a phenol, di-tert-butyl anisole, and a chelating agent such as ethylenediaminetetracetic acid to be useful in destroying gram positive and gram negative bacteria. Schemmel, R., Lynch, P., Krohn, K., and Kabara, J., Monolaurin as an Anticaries Agent, teaches the use of glycerol-monolaurin in inhibiting development of smooth surface caries

in rats innoculated with Streptococcus mutants. Kabara, Jr., Ohkawa, M., Ikekawa, T., Katori, T., and Mishikawa, Y., Examination on Antitumor, Immunological and Plant-Growth Inhibitory Effects of Monoglycerides of Caprylic, Capric, and Lauric Acids and Related Compounds, Pharmacological Effects of Lipids, Volume II, Pgs. 263-272 (1985) teaches the use of the monoglycerides or caprylic, capric and lauric acids for regulating antitumor, immunological, and plant-growth activity. Li, C., and Kabara, J., Effects of Lauricidin on Fomes Annosus and Phellinus Weirii, AOCS Monograph No. 5, Pgs. 45-47 (1978) teaches the use of monolaurin in combating root rot fungi in coniferous forest. Kenney, D., Cosmetic Formulas Preserved With Food-Grade Chemicals, Cosmetics and Toiletries, Part 1, Vol. 97, Pgs. 71-76 (1982) and Kabara, J. and Wernette, C., Cosmetic Formulas Preserved with Food-Grade Chemicals, Cosmetics and Toiletries, Part II, Vol. 97, Pgs. 77-84 (1982) teaches the use of monoglyceride emulsifier, food-grade phenols and a chelator in the preservation of cosmetics. Kabara, J., A New Preservative System For Food, Journal of Food Safety, Volume 4, Pgs. 13-25 (1982) teaches the use of monolaurin, a food grade phenolic, and a chelator as an antimicrobial for the preservation of food. Branan, A. and Davison, P. Antimicrobials in Foods, Marcel Dekker, New York 1983, Pgs. 109-140 teaches the use of saturated, unsaturated and esters of fatty acids as antimicrobials and the use of these compounds for food preservation. Kabara, J., Fatty Acids and Derivatives as Antimicrobial Agents - A Review, AOCS Monograph No. 5, Pgs. 1-14 (1978) teaches the use of saturated, unsaturated and esters of fatty acids as antimicrobials and the use of these compounds for permeating microorganism cellular membranes for killing the microorganism.

The art also teaches many methods of ethoxylation. Nonionic Surfactants, Schick, M.J., Marcel Dekker, Inc., New York (1966) and Dillan, K., Effects of the Ethylene Oxide Distribution on Nonionic Surfactant Properties, JAOCS, Vol. 62, No. 7, Pgs. 1144-1151 (1985) teach the ethoxylation of primary alcohols to product nonionic surfactants.

The above discussion clearly reflects the ambiguous state of the art with regard to the suitability and selection of fatty acid-based materials as antimicrobials, especially in the topical or preservative mode. The art disclosed materials vary widely in their efficacy and possess an even wider variety of side effects, particularly when employed in veterinary topical materials under adverse or stressful conditions. (The term glyceryl and glycerol are used interchangeably herein when describing fatty acid esters.)

The present invention relates to preservative pharmaceutical compositions and methods, especially those useful when applied topically and/or those which exhibit good shelf stability. The present invention relates to the discovery that the overall antimicrobial efficacy and pharmaceutical acceptability of certain glycerol fatty acid esters can be dramatically increased by either (1) the addition of certain ether groups, particularly ethoxy and propoxy units; (2) by use in combination with select fatty acid materials, (3) a combination of (1) and (2). Such modified glycerol fatty acid ester materials retain or exhibit an improved overall spectrum and speed of activity while producing fewer or reduced (in severity) side effects. Such a material is especially useful when compared to the unmodified material in that it produces much less irritation at the site of application.

The present invention further relates to the discovery that the spectrum and speed of activity of both modified and unmodified fatty acid esters can be significantly improved when used in a tertiary mixture or in combination with a mixture of two or more C<sub>6</sub>-C<sub>18</sub> fatty acids, preferably C<sub>6</sub>-C<sub>12</sub> fatty acids. All these materials are in turn employed in combination with a topical carrier. Such materials provide effective topical antimicrobial activity and are accordingly useful in the treatment and prevention of conditions which are caused, or aggravated by microbial organisms (including viruses) on skin and mucous membranes or are otherwise relates to microbes.

Also, the compositions of the present invention exhibit exceptional preservative applications. In addition to preserving the final composition and stabilizing the material to increase the efficacy in cold climate or conditions, the present compositions provide outstanding preservative characteristics when added primarily as a preservative in food stuffs, cosmetic formulations and pharmaceutical compositions (topical; parenteral; intramuscular; and intravenous). The preservative applications are further discussed in my copending patent application entitled "ANTIMICROBIAL PRESERVATIVE COMPOSITIONS", filed on the same day as the present application.

For example, such compositions are useful in veterinary applications as a teat dip, an eye medication and an ear medication. A safe and effective amount of the compositions, described above, to an animal in need of such treatment on the area to be treated one or more times daily.

It is well known that in general the ethoxylation or propoxylation of an antimicrobial agent generally renders that agent biologically inactive; at a minimum, the activity is substantially reduced. See Nonionic Surfactants, Martin J. Schick, Marcel Dekker, Inc., New York, New York Chap. 28, Pgs. 958-960.

Unexpectedly, it has been found that the addition of a select number of ethoxy or propoxy units to a glyceryl fatty acid ester results in an antimicrobial agent with good activity and reduced side effects.

Further, it has been discovered that the formed narrow ranged ethoxylates possess better surface-active properties when compared with the broad distribution range adducts. Also, the narrow range ethoxylates seem to act faster and have a better detergent activity than the broad distribution adducts; further, this fastener germicidal and detergent activity does not correlate with what is expected of non-ionic ethoxylates.

Generally, non-ionic ethoxylates such as TWEEW 80 and SPAN 20 are germicidally inactive. While not intending to be bound by theory, it appears that controlled ethoxylation or propoxylation adds to available hydroxyl radicals by ring cleavage with regeneration of the hydroxyl group. This reaction is an addition reaction without termination. Such ethoxylation is discussed in more detail in Dillan, K., Effects of the Ethylene Oxide Distribution of Nonionic Surfactant Properties, JAOCS, Vol. 62, Pgs. 1144-1151, 1985 which is herein incorporated by reference.

The glyceryl fatty acid ester which is to be ethoxylated or propoxylated for use in the compositions and methods of the present invention is preferably selected from the group consisting of polyhydric alcohols, polyglycerols, sucrose, glucose, sorbitol, propylenediol and glyceryl fatty acid esters having about six to about twenty-one carbon atoms. Such preferred compounds include monocaprylin, monocaprin, monolaurin, monomyristin, monopalmitolein,  $\alpha$ -monopalmitin, monostearin, monoolein, 1-monolinolein, 1-monolinolenin, and mixtures thereof. Still more preferred are monocaprylin, monocaprin, monolaurin, monomyristin, monopalmitolein, monoolein, monoicosenine and monoerucin and mixtures thereof. The highly preferred compounds include monocaprylin, monocaprin and monolaurin and mixtures thereof. Monolaurin is most highly preferred taking into account cost, availability and activity.

The glyceryl fatty acid esters are ethoxylated or propoxylated by conventional ethoxylating or propoxylating compounds and techniques. The compounds are preferably selected from the group consisting of ethylene oxide, propylene oxide, and mixtures thereof, and similar ringed compounds which provide a material which is effective. Most preferably, the ethoxylation compound is selected from the group consisting of ethylene oxide, propylene oxide and mixtures thereof.

The glyceryl fatty acid esters are ethoxylated or propoxylated under controlled conditions preferably within a narrow range according to conventional methods, such as those in the Dillan article further incorporated by reference. The glyceryl fatty acid esters are ethoxylated or propoxylated by a suitable amount of ethoxylate or propoxylate compound. In a preferred embodiment, the ethoxylation or propoxylation compound is reacted at a level of about 0.25 to about 25, more preferably about 0.5 to about 20 moles, more preferably, at about 0.5 to about 3.0 moles and, still more preferably, at about 0.5 to about 1.0 moles of ethoxylate or propoxylate per mole of glyceryl ester. Thus, the resulting products useful in the compositions and methods of the present invention generally contain at least about 1 mole of ethoxylate or propoxylate per four moles of glyceryl ester; in other words there is at least about one-quarter, and preferably at least about one-half, ether unit or moiety per glyceryl fatty acid ester unit or molecule. This could be further expressed as stating that useful ethoxylated glyceryl fatty acid esters of the present invention are esters wherein at least one-quarter, and preferably at least one-half of the total glyceryl ester has reunited with at least one ethoxy or propoxy moiety.

Generally, the adduct formed by the reaction of the glyceryl fatty acid ester and ethoxylation or propoxylation compound occurs as described in the art. However, it is noted that the reaction products are complex and may be formed by other well known conventional processes in the chemical art. For example, the glycerol portion and fatty acid portion may be ethoxylated or propoxylated separately prior to making the final ester.

The ethoxylation or propoxylation adds at least one-quarter, one-half or more ethoxy or propoxy units to the glyceryl fatty acid ester. Preferably the ethoxylation adds about 0.5 to 6, more preferably 0.5 to 3 and, still more preferably, 0.5 to 1 ethoxy or propoxy units per final unit of glyceryl fatty acid ester. This generally corresponds to about 0.5 to about 6 moles of ethoxy or propoxy compound per mole of glyceryl fatty acid ester.

The pharmaceutical compositions of the present invention employ a safe and effective amount of ethoxy/propoxy modified glyceryl ester adduct in combination with a suitable pharmaceutically-acceptable topical carrier. Such compositions preferably employ about 0.025 to about 20%, more preferably, about 0.1 to about 10% and, still more preferably, about 1 to about 5%, of the ester by weight of the carrier or final composition.

As discussed above, it has been further observed that a combination of a glyceryl fatty acid ester compound (either ethoxylated/propoxylated and non-ethoxylated/propoxylated) in a mixture with at least one and preferably two or more acids selected from the group consisting of  $C_6$ - $C_{18}$  fatty acids also demonstrates remarkable efficacy. Also, other polyols such as polyglyceryl, sucrose, glucose, sorbitol, and the like sugar esters have been found to work satisfactorily when substituted for the glyceryl fatty acid ester. The useful glyceryl fatty acid esters include those selected from the groups consisting of glyceryl fatty acid

esters having six to twenty-one carbon atoms and fatty acids having six to eighteen carbon atoms. The preferred glyceryl fatty acid ester compounds include monocaprylin, monocaprin, monolaurin, monomyristin, monopalmitolein,  $\alpha$ -monopalmitin, monostearin, monoolein, 1-monolinolein, 1-monolinolenin, and mixtures thereof. Still more preferred compounds include monocaprylin, monocaprin, monolaurin, monomyristin, monopalmitolein, monoolein, monoicosenoin, and monoerucin and mixtures thereof. The highly preferred compounds include monocaprylin, monocaprin, and monolaurin and mixtures thereof. These materials may also be modified by the addition of one or more ethoxy/propoxy units as described herein prior to being employed in the combination. The tertiary mixtures useful herein comprise a glyceryl fatty acid ester, (which may optionally be ethoxylated/propoxylated as described herein); a first fatty acid compound; and a second fatty acid compound. The preferred first and second fatty acid compounds for use in such tertiary mixtures or combinations are straight chain materials and include, without limitation, caproic, heptanoic, caprylic, pelargonic, capric, undecanoic, lauric, myristic, palmitic, heptadecanoic and stearic. The most preferred materials include caproic, heptanoic, caprylic, capric, undecanoic, and lauric. Highly preferred materials include heptanoic, caprylic and capric.

The glyceryl fatty acid esters, first fatty acid, and second fatty acid are added to a pharmaceutically-acceptable topical carrier in safe and effective amounts. In a preferred embodiment, they are present at a wt:wt ratio of ester: total fatty acid compounds of about 1:10 to about 10:1; more preferably about 1:10 to about 1:1, and still more preferably about 1:10 to about 1:15 with the glyceryl ester being present at a level of about 0.5 to about 5.0%; more preferably about 0.1 to about 2.0%; and still more preferably about 0.5 to about 1.0% of the final composition.

The glyceryl fatty acid esters may be ethoxylated or propoxylated under controlled conditions according to conventional methods, such as described above for use in the combination or mixture.

The compositions of the present invention can be prepared and applied in any suitable form, but are preferably prepared in forms including, without limitation aqueous solutions, lotions, balms, gels, salves, ointments, boluses, suppositories, and the like. Accordingly, the composition and methods may additionally employ conventional compatible pharmaceutically-acceptable carrier materials useful for such applications. It is desirable that the carrier selected be capable of codissolving or suspending the materials used in the composition. Carrier materials suitable for use in the instant composition, therefore, include those well-known for use in the cosmetic and medical arts as a basis for ointments, lotions, creams, salves, aerosols, suppositories, gels and the like. A preferred carrier generally comprised of alcohols, chelating agents, surfactants, parabens and water.

The alcohols useful in the compositions and methods of the present invention may be selected from the group consisting of propylene glycol, phenoxyethanol, methanol, ethanol, isopropyl alcohol, and mixtures thereof. In a preferred embodiment they are selected from the group propylene glycol, phenoxyethanol, and mixtures thereof; still more preferred is a mixture of propylene glycol and phenoxyethanol.

Surfactants useful in the compositions and methods of the present invention include those selected from the group consisting of sarcosinates, pluronic F68, sodium lauryl sulfate, sorbitan monolaurate, lauryldimethylamineoxide, lauric-diethanolamide, PEG-Esters (polyethylene glycol-dilaurate), coconut hydroxyethyl imidazoline, sodium sulfosuccinate ester of lauric MEA, sodium sulfosuccinate ester of ethoxylated lauryl alcohol, lauric-monoethanolamide, bis-(2-hydroxyethyl) cocoamine oxide IPA, bis-(2-hydroxyethyl) tallowamine oxide IPA, dimethylcocoamine oxide IPA, dimethylcocoamine oxide, (negative inhibitors), polyoxypropylene bases, coconut fatty acid, 2-sulfo-ester, sodium salt, N-coconut oil acyl-N-methyl taurine, sodium salt, lauroyl sarcosine, 30% sodium lauryl sarcosinate, sodium lauroyl sarcosinate, myristoyl sarcosine, oleoyl sarcosine, stearoyl sarcosine, polyoxyethylene 21 stearyl ether (0.1% BHA & 0.005% citric acid as preservatives), lauroamphoglycinate, lauroamphocarboxyglycinate, lauroamphocarboxypropionate, lauroamphocarboxyglycinate-sulfonate, sodium lauryl sulfate (66% lauryl, 27% myristyl, 71% cetyl), polyoxyethylene sorbitan mono-oleate, and mixtures thereof. In a preferred embodiment they are sarcosinates, amine oxides, pluronic F68, sodium lauryl sulfate, and mixtures thereof, more preferred are pluronic F68, sodium lauryl sulfate, amine oxides, and mixtures thereof.

Chelating agents useful in the compositions and methods of the present invention include those selected from the group consisting of EDTA, EDTA (Na)<sub>2</sub>, EDTA (Na)<sub>4</sub>, TEA, lactic acid, citric acid and mixtures thereof. In a preferred embodiment, they are lactic acid, citric acid, EDTA(Na)<sub>2</sub>, EDTA (Na)<sub>4</sub>, TEA, and mixtures thereof, more preferred are lactic acid, EDTA(Na)<sub>2</sub>, EDTA(Na)<sub>4</sub>, citric acid and mixtures thereof, highly preferred are lactic acid, EDTA(Na)<sub>2</sub>, EDTA(Na)<sub>4</sub>, and mixtures thereof.

Parabens useful in the compositions and methods of the present invention may be selected from the group consisting of methyl and propyl parabens. These may possess the methyl alone or in combination with 1-propyl paraben; 4 methyl 1 propyl; and mixtures thereof (and ester).

Water q.s. may form the remainder of the carrier and is selected from the group consisting of sterile water, distilled water, deionized water, tap and well water. In a preferred embodiment, they are sterile water, distilled water or deionized water. Emulsions may also be employed.

The alcohols discussed above may be employed in the compositions and methods of the present invention at any suitable level. In a preferred embodiment, they are present at a level of about 5 to about 60%, more preferred at about 10 to about 30% and, in a highly preferred embodiment, at about 20 to about 25%, by weight per volume of solution.

The surfactants discussed above may be employed in the compositions and methods of the present invention at any suitable level. In a preferred embodiment, they are present at a level of about 0.25 to about 10%, more preferred at about 2 to about 10% and, highly preferred, at about 4 to about 8%, weight per volume of solution.

The parabens discussed above may be employed in the compositions and methods of the present invention at any suitable level. In a preferred embodiment, they are present at a level of about 0.5 to 0.5%, more preferred, at about 0.1 to about 0.5% and, highly preferred, at about 0.1 to about 0.3%, weight per volume of solution.

The chelators discussed above may be employed in the compositions of the present invention at any suitable level. In a preferred embodiment, they are present at a level of about 0.05 to about 3%, more preferred at about 0.1 to about 0.5% and, highly preferred, at about 0.1 to about 0.2%, weight per volume of solution.

The compositions of the present invention may additionally employ adjunct components conventionally found in pharmaceutical compositions in their art-established fashion and at their art-established levels. Thus, for example, the compositions may contain additional compatible pharmaceutically active materials for combination therapy (such as supplementary antimicrobial, antipruritics, astringents, local anaesthetics, or anti-inflammatory agents), or may contain materials useful in physically formulating various dosage forms of the present invention, such as excipients, dyes perfumes, thickening agents, stabilizers, skin penetration enhancers, preservatives, or antioxidants.

Topical treatment regimens according to the practice of this invention comprise applying a safe and effective amount of the compositions described herein directly to the infected or at-risk skin or mucous membrane; particularly, in a veterinary use, on the teats, eyes, ear areas or at any other situs particularly susceptible to microbial contamination. The solution may be sprayed, dipped, wiped, dropped, poured, towelled, or the like, onto the area to be treated. Application can be made once, or preferably several times daily, to prevent bacteria, fungi, mold or the like from forming on the animal's skin, teats, ears and eyes.

The following examples illustrate the invention.

#### EXAMPLE 1

The following formulae have been found to be active against a substantial group of organisms. Also, these formulae have been found to be substantially non-irritating as an ear/eye preparation.

Ethoxylated Glycerol Monolaurin (Monolaurin EO)	0.05 - 1.0%
Caprylic Acid/Capric Acid Mixture	0.1 - 5.0%
Parabens	0.0 - 0.3%
Pluronic F68	1.0 - 10%
Phenoxyethanol	0.0 - 1.0%
EDTA (Na) <sub>2</sub>	0.05 - 0.3%
Water	82.4 - 98.65%

Glycerol monolaurin is ethoxylated by about one mole ethylene oxide per mole of glycerol monolaurin by conventional ethoxylation methods as described herein.

#### EXAMPLE 2

The following concentrate formula has been found to be active against a selective group of organisms, especially bovine mastitis. Also, the concentrate formula has been found to be non-irritating when applied as a teat dip.

Ethoxylated Glycerol Monolaurin	0.5 - 2.0%
Caprylic and Capric Acid Mixture	0.5 - 8.0%
Phenoxyethanol	0.0 - 2.5%
Propylene Glycol	10 - 30%
Parabens	0.0 - 1.0%
Pluronic F68	5 - 13.0%
EDTA (Na) <sub>2</sub> /Lactic Acid	1 - 15%
H <sub>2</sub> O	30 - 80% Monolaurin

is ethoxylated by about 0.5 to about 1.5 mole of ethylene oxide by conventional methods.

Also, the above formulas (Examples I and II) may be used in human or veterinary protocols, e.g., in the treatment of nasal tissue disease, ophthalmic disease, fungal corneal infection of horses, pulmonary disease, genital infections, and otitis externa. The formulas may be used in insecticidal or germicidal formulation on human or animal skin and plants, catheters, in egg washing, diapers, and wood preservatives. The formulas are also effective in combating fowl mites, ear mites, and ticks.

The above formulas are effective against yeasts, gram negative and gram positive organisms and protozoan, more particularly: C. albicans, C. parapsilosis, S. cerevisiae, E. coli, Ps. aeruginosu, S. epidermis, S. aureus, Bacillus subtilis, Streptococcus faecalis, Streptococcus pyogenec, Corynebacterium, Strep mutans, and Trichomonus vaginalis.

### EXAMPLE 3

The following formula concentrate was tested against a yeast, a gram negative and a gram positive organism:

	% Weight
(Monolaurin EO) Ethoxylated Glycerol Monolaurin	1.0
Caprylic and Capric Mixture	1.5
Propylene Glycol	22
Parabens	0.5
Phenoxyethanol	2.5
Pluronic F-68	5.0
EDTA (NA) <sub>2</sub>	2.0
dH <sub>2</sub> O	q.s.

After the formula was diluted 1:10 in water, the dilute was introduced to E. coli and to C. parapsilosis organisms. The results are as follows:

E. COLI	
Time	Colony Forming Units/ml
T <sub>0</sub>	4.3x10 <sup>6</sup>
T = 2 mins	<30
T = 10 mins	<30

C. PARAPSILOSIS	
Time	Colony Forming Units/ml
T <sub>0</sub>	1.7x10 <sup>6</sup>
T = 2 min.	2.5x10 <sup>3</sup>
T = 10 min.	<30

The formula of Example III was diluted 1:20 in water and then the dilute was introduced to *S. aureus*. The results are as follows:

S. AUREUS	
Time	Colony Forming Units/ml
T <sub>0</sub>	1.6x10 <sup>6</sup>
T = 2 min.	<5.0x10 <sup>1</sup>
T = 10 min.	<30

The above formula of Example III was diluted 1:8 with water and prophylactically applied to a cow's teats twice a day. As a result, upon analyzing the cow's teats, no substantial growth of micro-organisms was found on the teats. The same treatment was conducted on a cow's teats when the ambient air temperature was substantially below 40°F, and substantially similar results were found. It will be appreciated that substantial growth would normally be found.

#### EXAMPLE 4

Formula 4-1	
	% Weight
Monolaurin	1.0
( Monolaurin EO) Ethoxylated Glycerol Monolaurin	1.75
Caprylic and Capric Mixture	5.0
Pluronic F-68	13.0
EDTA (NA) <sub>2</sub>	4.0
H <sub>2</sub> O	75.25

Formula 4-2	
	% Weight
(Monolaurin EO) Ethoxylated Glycerol Monolaurin	1.75
Caprylic and Capric Mixture	6.0
Pluronic F-68	13.0
Lactic Acid (85%)	15.0
H <sub>2</sub> O	64.25

After the formulas of Example 4-1 and 4-2 were diluted 1:8 in water the dilute was introduced to *Strep Agalactial* and *Staph Aureus* organisms. The results illustrate the log reduction of organisms after two minutes of exposure with the dilute. Also listed are the log reduction results of other solutions used in the field.

Log Reduction of Organisms			
	Time	Strep Agalactial	Staph Aureus
Example 4-1	T = 2 min.	3.1	2.7
Example 4-2	T = 2 min.	4.3	5.1
Tegragon (Quaternary complex)	T = 2 min.	1.0	2.0
Teat Care (Chlorhexadine)	T = 2 min.	1.7	2.0
All Day (Sorbic Acid)	T = 2 min.	-	1.8
Quartermate (2000 Lodophor)	T = 2 min.	2.2	2.4



**EXAMPLE 5**

The following formula was tested against the identified organisms with the following results.

Formula 5	
	% Weight
(Monolaurin EO) Ethoxylated Glycerol Monolaurin	0.15
Caprylic and Capric Mixture	0.30
Parabens	0.05
Dowanol	0.1
Pluronic F-68	5.0
EDTA (Na) <sub>2</sub>	0.1
EDTA (Na) <sub>4</sub>	0.1
d H <sub>2</sub> O	94.2

Ps AERUGINOSA	
Time	Colony Forming Units/ml
T <sub>0</sub>	1.2x10 <sup>6</sup>
T = 2 min.	<30
T = 10 min.	<30

E. COLI	
Time	Colony Forming Units/ml
T <sub>0</sub>	3.0x10 <sup>6</sup>
T = 2 min.	<30
T = 10 min.	<30

**EXAMPLE 6**

The following formula was tested against the identified organism with the following results.

	% Weight
(Monolaurin EO) Ethoxylated Glycerol Monolaurin	0.15
Caprylic and Capric Mixture	0.30
Dowanol	0.10
Pluronic F-68	5.0
EDTA (Na) <sub>2</sub>	0.1
EDTA (Na) <sub>4</sub>	0.1
d H <sub>2</sub> O	94.25

Ps AERUGINOSA	
Time	Colony Forming Units/ml
T <sub>0</sub>	1.2x10 <sup>6</sup>
T <sub>2</sub>	<30
T <sub>10</sub>	<30

E. COLI	
Time	Colony Forming Units/ml
T <sub>0</sub>	3.0x10 <sup>6</sup>
T = 2 min.	< 30
T = 10 min.	< 30

While the above summarizes the present invention, it will become apparent to those skilled in the art that modifications, variations and alterations may be made without deviating from the scope and spirit of the present invention as described and claimed herein.

#### Claims

1. A topical antimicrobial pharmaceutical composition comprising a tertiary mixture comprising:
  - (a) a glyceryl fatty acid ester;
  - (b) a mixture of fatty acids comprising:
    - (i) a first fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
    - (ii) a second fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
  - (c) a pharmaceutically acceptable carrier.
2. A topical antimicrobial pharmaceutical composition according to claim 1 wherein the ratio by weight of the ester to the first and second fatty acids combined is 1:10 to 10:1.
3. A topical antimicrobial pharmaceutical composition according to claim 1 or 2 wherein the first fatty acid and/or the second fatty acid is a straight chain fatty acid having from six to twelve carbon atoms.
4. A topical antimicrobial pharmaceutical composition according to any one of claims 1 to 3 wherein the glyceryl fatty acid ester is a monoester.
5. A topical antimicrobial pharmaceutical composition according to claim 4 wherein the monoester contains 6 to 21 carbon atoms.
6. A topical antimicrobial pharmaceutical composition according to claim 5 wherein the monoester is monocaprylin, monocaprin, monolaurin, monomyristin, monopalmitolein, monolein, monoicosenoin, monoerucin or a mixture thereof.
7. A topical antimicrobial pharmaceutical composition according to any one of claims 4 to 6 wherein the monoester is present in an amount of 0.025 to 20.0% by weight of the composition.
8. A topical antimicrobial pharmaceutical composition according to any one of claims 1 to 7 in which the carrier comprises an alcohol, chelating agent, surfactant, paraben, water, or a mixture thereof.
9. A topical antimicrobial pharmaceutical composition according to claim 8 wherein the pharmaceutical carrier comprises an alcohol which is propylene glycol, phenoxyethanol, methanol, ethanol, isopropyl alcohol, or a mixture thereof; a chelating agent which is EDTA, Na<sub>2</sub>(EDTA), Na<sub>4</sub>(EDTA), TEA, lactic acid, citric acid or a mixture thereof; a surfactant which is a sarcosinate, an amine oxide, pluronic 68, sodium lauryl sulfate or a mixture thereof; or a paraben which is methyl paraben, propyl paraben or a mixture thereof.

10. A topical antimicrobial pharmaceutical composition according to claim 8 or 9 which comprises 5% to 60% by volume of the alcohol; 0.25% to 10% by weight of the surfactant; 0.05% to 5% by weight of the parabens; 0.05% to 4% by weight of the chelating agent.
- 5 11. A composition according to any one of claims 1 to 10 for use as a topical antimicrobial agent.
12. Use of a composition according to any one of claims 1 to 11 in the preparation of a topical antimicrobial medicament.

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(57) A topical antimicrobial pharmaceutical composition comprising a tertiary mixture comprising:

- (a) a glyceryl fatty acid ester;
- (b) a mixture of fatty acids comprising:
  - (i) a first fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
  - (ii) a second fatty acid antimicrobial agent which is a C<sub>6</sub>-C<sub>18</sub> fatty acid; and
- (c) a pharmaceutically acceptable carrier.

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# EUROPEAN SEARCH REPORT

Application Number

EP 92 11 9054

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL4)
X	PATENT ABSTRACTS OF JAPAN vol. 9, no. 82 (C-275)11 April 1985 & JP-A-59 216 577 ( KAO CORP. ) * abstract *	1-12	A61K31/20 A61K31/23
X	FR-A-2 097 036 (LAB.SOPHARGA) * page 3, line 31 - page 4, line 1 * Claim 1	1-11	
Y	PATENT ABSTRACTS OF JAPAN vol. 1, no. 54 (C-014)25 May 1977 & JP-A-52 015 818 ( TAIYKO KAGAKU ) * abstract *	1-12	
Y	US-A-4 002 775 (KABARA) * column 7, line 3 - line 9 * * tables 1-6 *	1-12	
Y	LIPIDS vol. 12, no. 9, pages 753 - 9 KABARA ET AL. * the whole document *	1-12	
E	EP-A-0 244 144 (KABARA) Claims	1-12	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. CL4)
Place of search THE HAGUE			Examiner P.GERLI
Date of completion of the search 02 FEBRUARY 1993			
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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